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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/658,824	09/08/2003	Stephen I. Rennard	UNMC/03017/0008	7805

7590 10/18/2005

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EXAMINER	
AFREMOVA, VERA	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 10/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/658,824	RENNARD ET AL.	
	Examiner	Art Unit	
	Vera Afremova	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/05/04;2/06/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of the group II, claims 11-19 in the reply filed on 8/05/2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-10 and 20-22 were canceled by applicants.

Claims 11-19 are under examination in the instant office action.

Information Disclosure Statement

The information disclosure statement filed 1/05/2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered in full.

Please, provide missing copies of the references 3 and 4 (IDS filed 1/04/2004).

Claim Rejections - 35 USC § 112

Claims 11-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11-14 and 19 are indefinite because it is not particularly clear what is a final product in a method for culturing embryoid bodies (EB), what type of EB differentiation is intended to be induced and when (or under what conditions, in what system) fibroblasts are produced.

Claim 16 recites the limitation "the differentiated cells" in the method for culturing EB. There is insufficient antecedent basis for this limitation in the claim 11.

Claims 15 and 18 are indefinite because it is unclear what is "ES qualified fetal bovine serum" and how/whether it is different from "fetal bovine serum".

Claim 18 is indefinite because it is unclear what is "knock out" DMEM and what is a meaning of term "knock out" with regard to the DMEM medium.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 11-13 and 16-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Dani et al. ["Differentiation of embryonic stem cells into adipocytes in vitro". Journal of Cell Science (1997), 110: 1279-1285].

Claims are directed to a method for culturing embryoid bodies (EB) from embryonic stem cells (ES) wherein the method comprises steps of obtaining ES, culturing ES to form EB, isolating EB and casting EB in a culture medium in 3D scaffolding material, growing EB in 3D environment and inducing differentiation of EB to produce fibroblasts after growing step. Some claims are further drawn to the use of differentiation-inducing "cytokines" including nicotinamide. Some claims are further drawn to isolating and culturing the "differentiated" cells in monolayers after growing EBs and after inducing differentiation of EBs. Some claims are

further drawn to the use of medium comprising DMEM and 10% serum (fetal bovine serum) for culturing differentiated cells or differentiated EBs.

The reference by Dani et al discloses a method for culturing murine embryoid bodies (EBs) derived from murine embryonic stem cells (ESc) wherein the method encompasses steps of obtaining murine ESc and culturing ESc in suspensions to form EBs, steps of growing EBs in a culture medium in 3D environment within a scaffolding material (3D plate) as 3D hanging drops or as 3D suspension; step of inducing differentiation of EBs to produce fibroblasts after growing step. For example: see page 1280, column 2, lines 12-21). After the growing and inducing steps the EBs are isolated and settled onto gelatin-coated plates for further culturing of differentiated cells in a differentiation medium (page 1280, column 1, par. 3, line 10). The culture medium contains MEM (page 1280, par. 2, lines 8) that is similar to DMEM medium and that provides nicotinamide (see ATCC catalogue, pages 516-517). Nicotinamide is required by the presently claimed method as a differentiation inducing "cytokine", for example: claim 13, lines 9. The differentiation medium for culturing the differentiated cells contains MEM and 10% selected fetal serum fetal (page 1280, column 1, par. 3, line 13).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11-13 and 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dani et al. ["Differentiation of embryonic stem cells into adipocytes in vitro". Journal of Cell Science (1997), 110: 1279-1285] taken with US 6,576,464 (Gold et al.).

Claims 11-13 and 16-18 as explained above. Claim 15 is further drawn to the use of medium with 2% serum at step of inducing differentiation of embryonic cells.

The reference by Dani et al. is relied as explained above. The cited reference discloses the use of 10% serum in both cultivation and differentiation medium in the method for culturing and differentiating embryonic cells.

However, US 6,576,464 teaches that differentiation of embryonic cells can be induced by withdrawal of serum or by substituting medium devoid of serum at the time of replating (col.16, lines 53-56). Thus, reduction of serum content in the medium intended for induction of differentiation would be an obvious protocol to ordinary skill practitioner at the time the claimed invention was made. One of skill in the art would have been motivated to reduce amount of serum for the expected benefits in inducing differentiation of embryonic cells as suggested by US 6,576,464. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention;

and

Claims 11-119 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

1. Specifically claims 11-14 and 19 are directed to a method for culturing EBs and inducing differentiating of EBs to produce fibroblasts in the presence of TGF-beta or in the presence of IL-4.

Contrary to the scope of the instant claims, the exemplified disclosure in the instant specification clearly describes and demonstrates that addition of TGF-beta or of IL-4 to the culture system with murine EBs does not result in production of fibroblasts, for example: see par. 0056 and 0057.

The state of prior art teaches and demonstrates that the presently claimed TGF-beta and IL-4 have been used for differentiation of EBs towards chondrogenic and hematopoietic cell lineages respectively. For example: see abstract of Schmitt et al. [Genes and Development

(1991) Vol. 5, No. 5, pages 728-740] and see abstract of Kramer et al. {Cytotechnology, (2003) Vol.41, No. 2-3, pages 177-187].

Thus, undue experimentation would be required to practice the invention as claimed due to the amount of experimentation necessary because of the limited amount of guidance and limited number of working examples in the specification, the nature of the invention, the state of the prior art, breadth of the claims and the unpredictability of the art.

Therefore, neither specification nor the prior art can be said to support the enablement of the claims 11-14 and 19 over their breath as drawn to the use of TGF or of IL-4 in the claimed method for culturing EBs and inducing differentiating of EBs into fibroblasts.

2. Claims 11-14 and 19 are directed to a method for culturing and inducing differentiating of generic EBs including human EBs into fibroblasts in the presence of FGF.

The generic disclosure in the instant specification does not point out what animals are source of embryonic cells. Thus, the generic description might encompass all animals including humans as source of embryonic cells. In one particular example the instant specification describes the appearance of fibroblast-like cells after growing murine EBs in the presence of FGF. The human model is not described in the instant specification.

The state of the prior art teaches and demonstrates that there are dramatic differences in development of primate and murine embryonic cells, that the usefulness of mouse ES cells for study of human development is limited (see US 5,843,780 entire document including col. 2, lines 5-9, especially) and that FGF is applied to maintain primate embryonic cells including human

embryonic cells in undifferentiated state (see 2003/0017589 entire document including par. 0013,especially).

Thus, undue experimentation would be required to practice the invention as claimed due to the amount of experimentation necessary because of the limited amount of guidance and limited number of working examples in the specification, the nature of the invention, the state of the prior art, breadth of the claims and the unpredictability of the art.

Therefore, neither specification nor the prior art can be said to support the enablement of the claims 11-14 and 19 over their breath as drawn to the use of FGF in the claimed method for inducing fibroblast differentiating of other than murine EBs or of generic EBs including primate and human EBs.

3. Specifically claims 11-14 are directed to a method for culturing EBs and differentiating EBs into fibroblasts in the presence of one selected "cytokine" as encompassed by claimed language "or" (claim 14, last line). The claimed list comprises a large variety of cytokines, growth factors, hormones, nutrients, etc that are used in animal cell culture media.

The reference by Schuldiner et al. teaches that none of the growth factors exclusively directs differentiation to only one cell type but rather alters relative proportions of specific cell types. For example: see abstract or Fig. 4 in the reference by Schuldiner et al ["Effects of eight growth factors on the differentiation of cells derived from human embryonic stem cells". PNAS. October 2000, Vol. 97, No. 21, pages 11307-11312].

Thus, undue experimentation would be required to practice the invention as claimed due to the amount of experimentation necessary because of the limited amount of guidance and

limited number of working examples in the specification, the nature of the invention, the state of the prior art, breadth of the claims and the unpredictability of the art.

Therefore, neither specification nor the prior art can be said to support the enablement of the claims 11-14 over their breath as drawn to the use of one selected "cytokine" from the presently claimed list to provide for exclusive and direct differentiation of EBs into fibroblasts.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

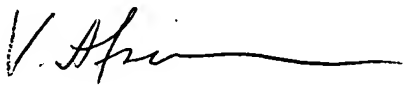
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached at (571) 272-0926.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova

AU 1651



October 13, 2005

VERA AFREMOVA

PRIMARY EXAMINER